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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	29+30

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/492,590	CARTENS, CARSTEN-PETER	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 18-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *29* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of a response to the previous office action, filed 6/18/2003 as Paper No. 28. The arguments made in the response have been considered in full and are addressed below. Acknowledgement is also made of a telephonic interview involving the examiner, applicant's representatives and George Elliot on 7/30/03. A summary of the interview (Paper No. 29) has been mailed along with this office action.

Claims 1-16 and 18-44 are pending in the instant application and stand rejected for the reasons of record that are repeated below. Any rejection of record not addressed or presented herein is withdrawn. This action is FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All of the rejections which follow and are of record are made over the teachings of Del Tito et al, which teaches the concept of analyzing the coding sequence for a desired protein, determining the presence of rarely used codons and compensating for the presence of the rarely used codons by co-expressing tRNA genes encoding tRNAs that correspond to the rarely used codons. The initial rejection made below is directed to include the broadest embodiments

encompassed by the rejected claims wherein the host cell is of *any* type (e.g. including those that are not E. coli) and the tRNA genes obtained from *any* source. It is made over the primary reference by Del Tito et al in view of prior art cited by applicants as demonstrating rare codon usages had been calculated for thousands of different species at the time of filing and that a large number of tRNA genes corresponding to these rarely used codons were known. The rejections that follow are made over the more specific embodiment, exemplified in the instant specification, where the host cell is E. coli and a heterologous coding sequence comprising more than two types of rarely used codons is expressed in E. coli. The outstanding rejection of claims 39-44 as being obvious over Del Tito et al alone, originally made in Paper No. 12, has been withdrawn as it is redundant to the initial rejection made below (originally presented in Paper No. 25).

Claims 1-5, 10-16, 22-23, 26-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Tito et al (U) in view of Nakamura et al (U2), Zhang et al (V2), Saier et al (W2), Sprinzl et al (X2), Kawakami et al (U3) and Clouthier et al (V3). **This rejection is maintained for reasons of record in Paper No. 25, mailed 12/18/02 and repeated below**

Del Tito et al teach the construction and use of a plasmid, pRI952, which comprises an array of two tRNA genes (argU and IleX) encoding tRNAs specific for the rarely used codons AGG/AGA and AUA, respectively (e.g. page 7087, paragraph 2; Tables I and II). The authors teach that pRI952 was constructed by insertion of a PCR-amplified DNA comprising the gene for ileX flanked by HindIII restriction sites into pDC592, a pACYC184 derivative (i.e. low copy number plasmid) already possessing the argU gene (e.g. pages 7087, column 2, paragraph 2). Del Tito et al teach that coexpression of the two tRNA genes along with the gene encoding the

heterologous polypeptide Mup^r IRS results in increased levels of active protein as compared to a control in which no additional tRNA genes are expressed or as compared to cells comprising a plasmid only expressing the ileX gene (e.g Table II). Del Tito et al teach that "...problems in expression can be avoided by a careful inspection of the coding sequence and inclusion of appropriate tRNA genes or necessary site-specific mutations." (page 7087, column 1, paragraph 2). The authors conclude that the co-expression of minor tRNAs such as ileX or argU can be utilized to overcome translational stresses due to the presence of rarely used codons within the coding sequence for a gene of interest (e.g. page 7091, column 1, paragraph 3). Del Tito et al teach the purification by reverse-phase HPLC of another heterologous polypeptide (i.e. the B/LeeHA antigen) produced by their system for compensating for the presence of rare codons in the coding sequence for the desired polypeptide (e.g. page 7088, column 1, paragraphs 3-4).

Del Tito et al do not explicitly teach the use of a vector comprising an array of two or three or more tRNAs corresponding to rarely used codons for overexpression of a heterologous gene comprising rarely used codons for any species other than E. coli.

Nakamura et al (Nucleic Acids Research, 1996, Vol. 24, pages 214-215; see the entire reference) provide codon usage data tabulated from the GenBank international DNA sequence databases for 4,805 species (e.g. prokaryotes, protozoa, fungi, animals and plants).

Zhang et al (Gene, 1991, pages 61-72, see the entire reference) detail low usage codons in species as diverse as E. coli, yeast, Drosophila and primates.

Saier, M. H. (FEBS, 1995, Vol. 362, pages 1-4; see the entire document) teaches the rare codon usage in several different species (e.g. R. capsulatus, R. speriodes, C. acetobutylicum, S. coelicular and E. coli).

Sprinzl et al (Nucleic Acids Research, 1984, Vol. 12, supplement, pages r89-r130); see the entire document) teach a compilation of 353 sequences of tRNA genes including cellular and mitochondrial tRNAs from bacteria and phage, plants, yeasts and fungi, insects, amphibians and mammals, including rats, mice, cows and humans.

Kawakami et al (1993, Genetics, Vol. 135, pages 309-320; see the entire document) teach a rare Arg-tRNA-CCU in S. cerevisiae).

Clouthier et al (J. Bacteriology, 1998, Vol. 180, pages 840-845, see the entire document) teach a rare Arg-tRNA-AGA from S. enteritidis.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the vector construct taught by Del Tito et al for compensating for the presence of rarely used codons present in the gene encoding a protein of interest by interchanging and/or adding different tRNA genes corresponding to other rarely used codons in a given cell type, because Del Tito et al teach that it is within the skill of the art to carefully scrutinize the coding sequence of a protein, identify rarely used codons and compensate for the presence of such rare codons by supplying in trans the tRNA corresponding to the identified rarely used codons from a vector expressing different tRNA genes, and because the rarely used codons and corresponding genes were widely known in the art (i.e. the teachings of Nakamura et al, Zhang et al, Saier, Sprinzl et al, Kawakami et al and Clouthier et al). One would have been motivated to do so in order to meet the particular rare-codon requirements of a gene encoding a desired protein in combination with a given cell type, and thus receive the expected benefit of increasing its expression in the given cell type, as taught by Del Tito et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing any tRNA gene

obtained from any cell type that was known in the art (i.e. ileY, proL, leuW, etc.) in the approach taught by Del Tito et al to increase the production of a desired protein that comprises rarely used codons.

Claims 1-5, 10-16, 22-23 and 26-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Tito et al (U) in view of Makoff et al (V). **This rejection is maintained for reasons of record in Papers No. 12 and 25, mailed 5/9/01 and 12/18/02, respectively. The grounds for the rejection are repeated below.**

The teachings of Del Tito et al are described above and are incorporated here, except:

Del Tito et al do not explicitly teach the use of a vector comprising an array of 3 or more tRNAs corresponding to rarely used codons for overexpression of a heterologous gene comprising rarely used codons. Del Tito et al do not explicitly teach the use of ileY, proL, and leuW.

Makoff et al teach that the expression of the tetanus toxin fragment C in E. coli is limited by its high demand for rare tRNA molecules (page 10193, paragraph 2). Makoff et al teach that fragment C comprises several different rare codons specifying different amino acids (i.e. Leu, Ile, Ser, Pro, Arg and Gly) that are fairly evenly spread out through the coding sequence (Table 2; page 10196, paragraph 2). Makoff et al teach that replacement of almost the entire coding sequence with a synthetic sequence which lacks the rarely used codons results in an approximate 4-fold increase in expression of the desired heterologous polypeptide (page 10199, paragraph 2). Makoff et al teach that fragment C from tetanus toxin shows considerable promise as a subunit vaccine against tetanus (page 10193, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the vector taught by Del Tito comprising argU and ileX for increasing the expression of a desired heterologous polypeptide whose gene comprises rarely used codons by introducing additional tRNA genes corresponding to rarely used codons other than AGA, AGG, or AUA in order to express the tetanus fragment C subunit in E. coli because: 1) Del Tito et al teach it is within the skill of the art to express tRNA genes corresponding to different rarely used codons from the same vector in order to compensate for the presence of the rarely used codons in a gene encoding a desired polypeptide, 2) because Makoff et al teach it is within the skill of the art to increase the expression of fragment C in E. coli by compensating for the presence of a number of different rarely used codons in the gene encoding fragment C, and 3) because tRNA genes corresponding to the rarely used codons in the fragment C coding sequence were known in the art. One would have been motivated to do so in order to receive the expected benefit of expressing increased levels of fragment C from the native gene encoding fragment C without having to synthetically construct a gene encoding fragment C that lacks the rarely used codons. Based upon the combined teachings above, and absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing a vector made from the combined teachings above comprising 3 or more tRNA genes corresponding to the rare codons present in the coding sequence for fragment C, as taught by Makoff et al, to overexpress fragment C from its native genes in E. coli.

With regard to the different tRNA genes recited in the rejected claims (e.g. ileY, proL or leuW), it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate any tRNA gene known in the art into the vector made from the combined

teachings above in order to provide the necessary tRNAs to compensate, as taught by Del Tito et al, for the presence of the rarely used codons present in the fragment C gene, as taught by Makoff et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing such tRNA genes in the expression system made from the combined teachings above in order to increase the levels of expression of fragment C in E. coli.

Claims 6-9, 19, 21 and 24-25 are rejected under 35 U.S.C. 103(a) as being obvious over Del Tito et al (U) in view of Makoff et al (V) as applied to claims 1-5, 10-16, 22-23 and 26-38 above, and further in view of the 1997 Novagen catalog (pages 42-44) (W). **This rejection is maintained for reasons of record in Papers No. 12 and 25, mailed 5/9/01 and 12/18/02, respectively. The grounds for the rejection are repeated below.**

The teachings of Del Tito et al and Makoff et al are described above and are applied as before, except: Del Tito et al teach that the expression of tRNA genes has been shown to be deleterious to the host cell and that for this reason the ileX promoter was used to control expression of the ileX gene from low-copy number plasmids (page 7090, column 2, paragraph 3).

Neither reference teaches the use of a vector in which the expression of the tRNA genes is regulated by an IPTG inducible promoter, the use of a T7 RNA polymerase promoter, or protease deficient cells.

The 1997 Novagen catalog (pages 42-44; Figure 1) describes a T7 RNA polymerase expression system for tight control over the expression of toxic genes in E. coli. The system features: 1) the use of a phage λ lysogen (DE3) that comprises the gene encoding T7 RNA

polymerase under control of an IPTG-inducible promoter, 2) a T7lac promoter that is also inducible upon addition of IPTG and 3) an E. coli strain which lacks functional genes for the Lon and OmpT proteases (e.g. page 43, paragraph 2; page 44).

It would have been obvious to one of ordinary skill in the art at the time of the invention to clone the tRNA genes for tRNAs corresponding to rarely used codons used in the methods made from the combining teachings above into one of the pET vectors/expression systems described in the 1997 Novagen catalog because Del Tito et al teach it is within the skill of the art to compensate for the presence of rarely used codons in the gene for a desired polypeptide by expressing the corresponding tRNA genes from a vector in E. coli, because Del Tito et al also teach that the expression of tRNA genes in E. coli can have a negative effect on the host cell and because the T7 RNA polymerase-based system described in the Novagen catalog for tightly controlled expression of target, toxic genes in E. coli was well known and widely used within the art for the expression of toxic genes in E. coli. One would have been motivated to do so in order to receive the expected benefit of avoiding any potential toxic effects associated with the expression of the tRNA genes in E. coli. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing the pET expression system for the controlled expression of tRNA genes in E. coli for the purpose of expression of desired polypeptides whose coding sequence comprises a number of different, rarely used codons.

Claims 18 and 20 are rejected under 35 U.S.C. 103(a) as being obvious over Del Tito et al (U) in view of Makoff et al (V) and the 1997 Novagen catalog (pages 42-44) (W) as applied to claims 1-17, 19 and 21-38 above, and further in view of Wnendt (X). **This rejection is**

maintained for reasons of record in Papers No. 12 and 25, mailed 5/9/01 and 12/18/02, respectively. The grounds for the rejection are repeated below.

The teachings of Del Tito et al, Makoff et al and the 1997 Novagen catalog are described above, and applied as before, except:

The cited references do not teach the use of endA$^-$ E. coli strains.

Wnendt teaches that the use of endA$^-$ strains allows for greater and higher quality yields of plasmid DNAs from bacterial cells (page 270, column 1, paragraph 1).

It would have been obvious to one of ordinary skill in the art at the time of invention to introduce an endA$^-$ mutation into the strain of E. coli used in the methods made from the combined teachings above to express heterologous polypeptides whose genes comprise different rarely-used codons because Wnendt teaches that the lack of an EndA nuclease activity results in higher quantity and quality of plasmids isolated from E. coli strains that are endA$^-$. One would have been motivated to do so in order to increase the yield and quality of plasmids recovered from the host cells during cloning of the vectors comprising the tRNA genes corresponding to the rarely used codons present in the gene encoding a desired polypeptide. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing an endA$^-$ strain of E. coli in methods made from the combined teachings above for expression of a gene encoding a desired polypeptide comprising rarely used codons.

Response to Arguments/Obviousness Rejections

Applicant's arguments filed in Paper No. 28 have been fully considered but they are not persuasive. The response continues to argue that the claimed inventions are not obvious over the

prior art described above due to the commercial success of two Stratagene products that meet the claim limitations (i.e. cells comprising RIL and RP tRNA gene arrays; see the two Buchanan declarations, Papers No. 10 and 15). The response filed in Paper No. 28 essentially argues: 1) the commercial success of the claimed invention provides an objective indication of nonobviousness sufficient to overcome the rejections, 2) commercial success is an established indicator of nonobviousness and must be taken into account in considering the issue of obviousness, 3) that evidence of such success is secondary in time does not mean it is secondary in importance, 4) a showing of commercial success is relevant in resolving the issue of nonobviousness, 5) the law does not impose a standard that there must be a product on the market embodying the exact prior art before commercial sales figures can be considered an indicator of non-obviousness, 6) the absence of a commercial embodiment of the prior art composition would, if anything, support the non-obviousness of a claimed product for which there are significant sales (i.e. the absence of a commercial product embodying Del Tito's construct is simply further indicative of non-obviousness), 7) sales figures for the two constructs described in the two Buchanan declarations demonstrate a 2.73 ratio in favor of the three tRNA gene array versus the 2 tRNA gene array, 8) this difference in sales indicates that the three tRNA gene array is nonobvious over the two tRNA gene array, 9) one need not show all possible elements within the claims were successfully commercialized in order to rely upon the success of the embodiment commercialized to overcome alleged obviousness, 10) the question is not whether commercial success would necessarily be realized for other embodiments, but whether the commercial success of the commercialized embodiments is sufficient to demonstrate nonobviousness.

To the extent that the arguments presented in Paper No. 28 are restatements of arguments made previously, the responses made by the examiner in Paper No. 12 (mailed 3/9/01), Paper No. 19 (mailed 3/26/02) and Paper No. 25 (mailed 12/18/02) are applicable and incorporated herein by reference. With regard to the statements concerning the relevance of a showing of commercial success to determining obviousness over the prior art, at no point has the examiner indicated that a demonstration of commercial success is not relevant to determining obviousness of the claimed invention over the prior art. Nor has the examiner ignored the arguments presented thus far as to the purported commercial success of the Stratagene products. Applicant's data and arguments concerning the commercial success of the Stratagene host cells/vectors have been considered throughout prosecution to date, but have been found unconvincing with regard to 1) establishing the sales figures presented in the first Buchanan declaration (Paper No. 10) are actually due to something in the invention that was not already known and available in the art, 2) establishing that the sales figures for the two products shown are commensurate in scope with what is claimed, 3) that any commercial success that may have been demonstrated is so great as to make the invention unobvious over the prior art.

With regard to arguments concerning the background against which the examiner must judge commercial success, the examiner has not imposed at any point a standard wherein a product meeting the exact limitations of the rejected claims must already be on the market. The examiner has indicated, however, that it is difficult to judge the *degree* of any success for applicant's vectors comprising an array of two or three tRNA genes corresponding to rarely used codons because there was apparently no other system on the market for the time applicants have presented sales figures which was directed towards expressing nucleic acids comprising rarely

used codons. Nor has applicant presented any sales figures for the same competent cells lacking the tRNA genes so that one might compare the level of sales of cells of the same type whose purchase is not affected by the presence of the tRNA gene arrays. The examiner agrees with arguments made by applicant's representatives in a telephonic interview on 7/30/03 (see Paper No. 29) that such a comparison would be "apples to oranges", but it would at least provide some background against which to judge the sales figures presented in the first Buchanan declaration (Paper No. 10). Applicants do point out in the first Buchanan declaration that the competent cells comprising the arrays of tRNA genes are 44% more expensive than those same cells lacking the tRNA arrays, and that it is probable that the reason one would pay the extra money for the more expensive cells is the presence of the tRNA genes corresponding to rarely used codons. This is a reasonable statement, but is only circumstantial evidence for a nexus between the sales figures reported in Paper No. 10 and the presence of tRNA genes on the Stratagene vectors, so that whatever success has been observed cannot be unequivocally attributed to the presence of the tRNA genes.

The assertion that the absence of any other commercial expression system featuring tRNA genes corresponding to rarely used codons is somehow evidence that the claimed invention is unobvious is unsupportable. First, the examiner knows of no legal basis for concluding that being the first to put a product into the market place is evidence of unobviousness over the prior art. Second, there is no way for the examiner to determine why other companies might have been delayed in getting a particular product to market (e.g. other business concerns, etc.). For example, there is evidence of record that others were developing similar systems for market at about the same time that Stratagene was developing their system.

In a 37 CFR 1.131 declaration presented in Paper No. 15, applicant has "sworn behind" the Zdanovsky et al patent, U.S. Patent No. 6,214,602, assigned to the Promega Corporation. The examiner has no way of knowing why Promega was not the first to put an analogous system for expressing a nucleic acid having rarely used codons into the market place (e.g. a system based on the specific vectors recited in the issued claims).

Applicant's rather novel argument that the sales data for cells comprising a 3 tRNA gene array versus cells comprising a 2 tRNA gene array makes the 3 tRNA gene array unobvious over the prior art is interesting, but not persuasive on at least two grounds. While it is true that this is less of an "apples to oranges" comparison than comparing the sales data for competent cells comprising tRNA gene arrays to sales data for the same cells lacking such tRNA gene arrays, it is still somewhat of an "apples to oranges" comparison. The fact that Stratagene's 2 gene array (i.e. RP= argU, proL) comprises proL while the 3 gene array (RIL= argU, ileY, leuW) does not, and that the 3 gene array comprises 2 tRNA genes not present on the 2 gene array, raises the question as to whether the difference in sales numbers is due more to the *nature* of the tRNA genes on the arrays rather than the *number* of genes on the arrays. Thus, one cannot conclude that the difference in sales is necessarily due to the presence of 3 tRNA genes versus 2 tRNA genes.

Second, even if one concludes that the difference in sales is due to the presence of an additional tRNA gene, the evidence presented is not of sufficient degree to overcome the obviousness rejections made above. Del Tito et al teach that "...problems in expression can be avoided by a careful inspection of the coding sequence and inclusion of appropriate tRNA genes or necessary site-specific mutations." (page 7087, column 1, paragraph 2). Thus, Del Tito et al

clearly teach the basic concept that one can overcome problems expressing a heterologous nucleic acid sequence due to the presence of rarely used codons by coexpressing tRNA genes corresponding to those rarely used codons. Increasing the number of tRNA genes present on the plasmids taught by Del Tito, or other expression plasmids known in the art, cannot be considered as novel because there is no evidence of record that it would not have been expected that one could do so, and because the art already teaches that one can express at least three gene products from a single plasmid vector of the type used by Del Tito et al (e.g. the vectors taught by Del Tito et al also express at least one selection marker). Therefore, a simple 3-fold difference in sales cannot be persuasive that the claimed invention is unobvious over the art of record.

At no point has the examiner suggested that applicant needs to show commercial success for all possible embodiments embraced by the claims in order to overcome alleged obviousness. The examiner has, however, correctly pointed out that a demonstration of commercial success for two embodiments does not necessarily make all other embodiments embraced by the rejected claims unobvious (i.e. the commercial success needs to be commensurate in scope with the claims). The rejected claims read on any host cell comprising any combination of three or more, or two or more, tRNA genes corresponding to rarely used codons. Even if the claimed embodiments were limited to E. coli, it is not at all clear that a demonstration of commercial success, for example, for a 3 gene array comprising argU, ileY and leuW (e.g. Stratagene's RIL strains) would make unobvious an E. coli cell comprising any other combination of 3 or more tRNA genes. How then can one expect that the same degree of commercial success would be expected for an embodiment that does not feature E. coli or features tRNA genes corresponding

to rarely used codons from cell types other than E. coli? Again, a demonstration of commercial success must be commensurate in scope with that which is claimed (MPEP 716.03(a)).

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
July 31, 2003